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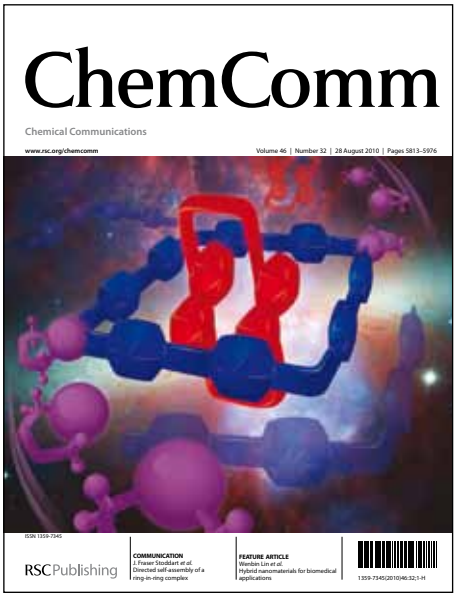

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Palladium catalyzed dehydrogenative arylation of coumarins: An unexpected switch in regioselectivity†

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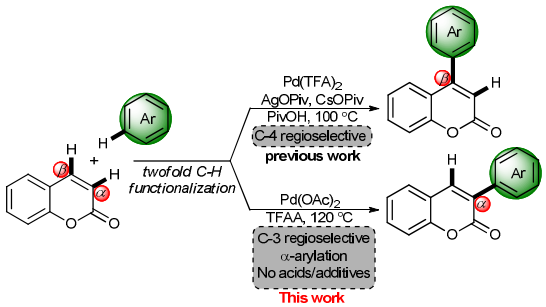
A new regioselective α-arylation of coumarins with unactivated simple arenes via a palladium-catalyzed twofold C-H functionalization is devised. This method offers an attractive new approach to a wide variety of 3-arylcoumarins from readily accessible starting materials.

Direct functionalizations through metal-catalyzed double C–H activation reactions have begun to emerge as an alternative route for C-C bond formation.[1] A direct arylation approach allows for construction of carbon-carbon bonds without the need for prior functionalization of coupling partners *via* metalation. This protocol saves synthetic steps and serves as an elegant example of atom economy approach. In context with this, scope of palladium-catalyzed twofold C-H functionalization has been expanded to a plethora of arenes.[2]

In light of the progresses in direct arylation of heterocycles, which in most cases encounter the difficulties associated with controlling the regioselective C–H bond activation,[3] our interest in functionalization of coumarins motivated us to explore site-selective dehydrogenative arylation of these privileged scaffolds. Many naturally-occurring and synthetic compounds featuring a 3-arylcoumarin scaffold are known to manifest notable biological and pharmaceutical activities which include antimicrobial, antibacterial, anti-inflammatory, antioxidant, anti-HIV and very recently, anticancer activities.[4] As a result of their expressive structural diversity, they also have found some possible applications in treatment of allergic disorders, as Hsp90 C-terminal inhibitors and strong inhibitors of antigen-induced RBL-2H3 mast cell degranulation.[5]

Very recently we and other groups developed a C-4 regiocontrolled direct arylation of coumarins using arylboronic acids.[6] The strategy was further improved by Hong et al. which disclosed a palladium–pivalic acid combination for arylation of coumarins with arenes through double C–H bond activation (Scheme 1).[7] 3-Arylated coumarins were not observed and the regioselectivity was in bias of *β*-arylation which is an expected regioselectivity in Heck type reactions. Direct installment of arenes at α-position of a coumarin ring via a twofold C-H bond functionalization which in terms of high synthetic efficiency would be the most desirable strategy for construction of 3-arylcoumarins however, continues to be problematic and elusive. Some focused efforts on construction of 3-arylcoumarins applying prefunctionalized coupling partners include Suzuki cross-coupling of boronic acids/esters with halocoumarins,[8] Negishi reaction of zincated coumarins[9] and cross-coupling of coumarins and iodoarenes.[10] We also have recently reported a palladium-catalyzed decarboxylative arylation of coumarin-3-carboxylic acids with iodoarenes where the carboxylate group at C-3 warranted the regioselectivity.[11] The liabilities of prefunctionalization of at least one of the coupling partners to overcome regioselectivity and chemoselectivity issues however, have limited the applicability of these procedures. One might therefore expect that versatile atom- and step economic routs for construction of these frameworks would find significant utility in organic synthesis.



Scheme 1 Switch in regioselectivity

Herein, we set out to explore an unprecedented C-3 selective dehydrogenative cross-coupling of coumarins and simple non-activated arenes (Scheme 1). This protocol simply joins two different sp^2-hybridized carbon centers with excellent site-selectivity without the requisite for installment of disposable functionalities. Remarkably, no acids were required and trifluoroacetic anhydride as a promising alternative proved to be effective as the sacrificial oxidant and solvent. This protocol fulfills the objectives of straightforward site-selective construction of biologically attractive 3-arylcoumarin backbones in an economically viable and environmentally attractive manner.

Our initial attempts to couple coumarin **1a** and pentylbenzene **2a** under a combination of $Pd(OAc)_2$/PivOH which is known to be effective in lowering arenes C-H bond cleavage energy, was unsuccessful (Table 1, entry 1). Various carboxylic acids as sources of catalytic carboxylate bases including AcOH, $EtCO_2H$ and 2-picolinic acid also were all not effective (see SI). When TFA was used however, selective arylation of coumarin at C-3 was pleasingly achieved albeit in 32% yield (entry 2). Other palladium species screened further, were ineffective in promoting the reaction (entries 3-5). As the terminal oxidant's properties were proved to be critical to the coupling efficiency in C-H activation reactions, a subsequent optimization of oxidants were conducted. Among various oxidants screened, $K_2S_2O_8$ proved to be most effective

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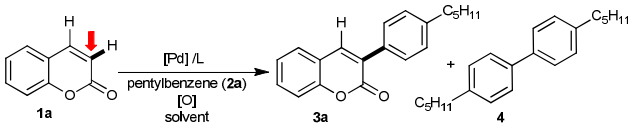
Table 1 Optimization of direct arylation reaction[a]



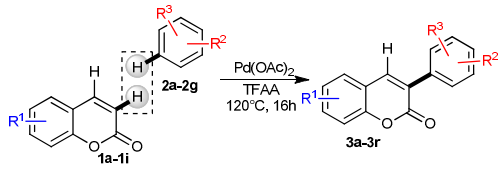
Entry	Catalyst	[O]	Solvent	Yield (%)	
				3a	**4**
1	$Pd(OAc)_2$		$^tBuCO_2H$	trace	12
2	$Pd(OAc)_2$		TFA	32	10
3	$PdCl_2$		TFA	8	10
4	$Pd(acac)_2$		TFA	12	15
5	$Pd(dba)_2$		TFA	trace	15
6	$Pd(OAc)_2$	TBHP	TFA	49	15
7	$Pd(OAc)_2$	BPO	TFA	47	25
8	$Pd(OAc)_2$	O_2	TFA	40	15
9	$Pd(OAc)_2$	$K_2S_2O_8$	TFA	51	5
10	$Pd(OAc)_2$	$K_2S_2O_8$	TFA/TFAA	58	5
11	$Pd(OAc)_2$	$K_2S_2O_8$	TFAA	63	5
12	**$Pd(OAc)_2$**		**TFAA**	**62**	**5**
13	$Pd(OCOCF_3)_2$		TFAA	61	7
14	$Pd(OAc)_2$		TFAA/DMA	15	10
15	$Pd(OAc)_2$		TFAA/DCB	50	20

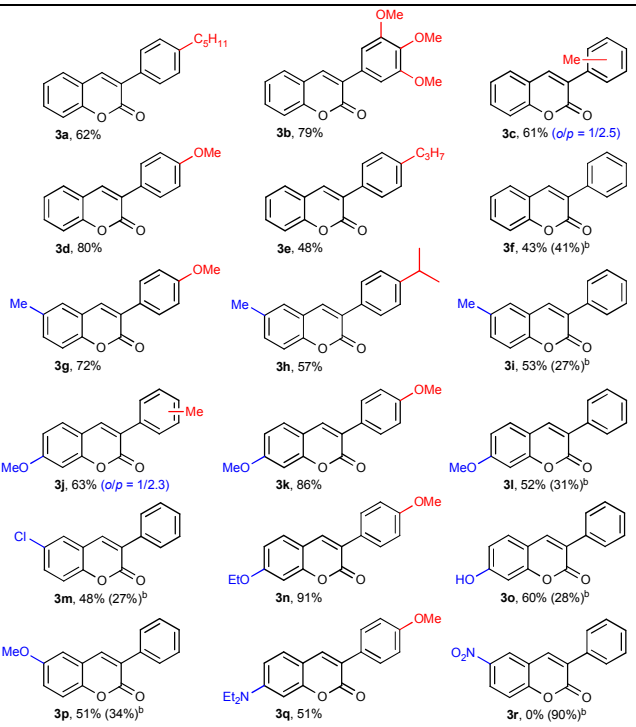
[a]Reactions conditions: coumarin **1a** (1 equiv), pentylbenzene **2a** (6 equiv), catalyst (10 mol %), oxidant (1 equiv), TFA (13 equiv), TFAA (1 equiv), solvent (0.5 M), 120 °C for 16 h.

(entries 6-9). A combination of TFA/TFAA further improved the yield to 58% (entry 10). Surprisingly, when TFA was removed, comparable yield was obtained even in absence of the oxidant (entries 11-12). The reaction also proceeded well with $Pd(TFA)_2$ as catalyst and comparable yield was obtained (entry 13). With a combination of TFAA and other solvents such as DMA, DCB and ACN, the conversions proved to be unsatisfactorily low (see SI). Gratifyingly, combination of $Pd(OAc)_2$/TFAA proved to be an optimal combination for reasonably selective arylation of coumarin at C-3 where, a 62% isolated yield of the desired product **3a** was obtained with no traces of 4-arylcoumarin. Furthermore, the reaction was also regioselective in functionalization of arene in a manner that only more sterically accessible para C–H was functionalized.

With the optimum condition in hand, we next sough to explore the scope of twofold C-H activation reaction for construction of 3-arylcoumarins. Accordingly a variety of coumarins and arenes possessing electron-donating and withdrawing groups were employed (Table 2). Results showed that various groups including alky, methoxy, amine and hydroxyl groups were tolerated and the reactions were highly regioselective where, almost in all cases 4-arylcoumarins were not observed. Replacing pentylbenzene with more electron rich arenes such as trimethoxybenzene and anisole promoted the coupling reaction more efficiently and 3-arylcoumarins **3b** and **3d** were obtained as the major regioisomer in yields exceeding 79%. With toluene however, a mixture of *o*- and *p*-substituted regioisomeric products **3c** was obtained in a combined 61% yield (*o*/*p* = 1/2.5). Propylbenzene and benzene also resulted related adducts **3e** and **3f**, albeit in moderate yields. Various substituted coumarins also were found to be amenable to this direct C-H functionalization reaction. Arylation of alkyl and alkoxy substituted coumarins proceeded smoothly leading to 3-arylcoumarin scaffolds **3g-3l**

Table 2 Scope of regioselective arylation of coumarins[a]





[a]All reactions were run under the optimized reaction conditions. [b]Recovered starting materials in parantheses

in 52-86% yields. The highest yield was obtained in transformation of 7-ethoxycoumarin to its related adduct **3n** where an almost quantitative yield was established. Coumarin with a chloride substituent also went through the arylation reaction and resulted **3m** with intact halo group to serve as a good precursor for further functionalizations. We were pleased to see that even sensitive functionalities such as hydroxyl groups were also tolerated and the coupling reactions were proceeded with no requisite for protection of these groups (**3o**). This feature is ubiquitous in hydroxycoumarin based biologically active products, which eliminates the requirement of protection and deprotection of hydroxyl groups. Hydroxylated 3-arylcoumarins especially those with the hydroxyl group at C-7, are proved to exhibit antiproliferative, apoptosis-inducing and cell cycle arrest activities. They also show different cytotoxic values according to the positions of the OH-groups in their structures.[12] With an amine substituent also a satisfactory yield was gained (**3q**, 51%). Coumarins bearing a NO_2 group unfortunately proved to be not a good substrate for this cross-coupling reaction.

A possible mechanism for his transformation is outlined in scheme 2. Formation of $Pd(TFA)_2$ from $Pd(OAc)_2$ in the presence of trifluoroacetic anhydride[13] and subsequent conversion to highly electrophile species $Pd(OCOCF_3)^+$ is expected.[14] Next, electrophilic attack of coumarin on

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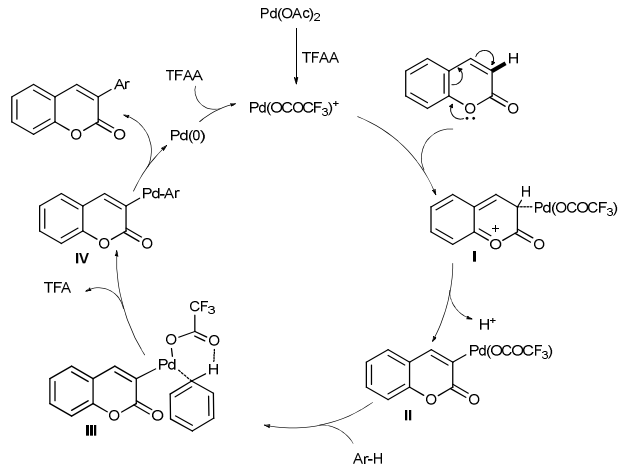
palladium at the more favorable C-3 position due to its nucleophilic character results in C-3 palladated species **II**. Subsequent coordination with arene and C-H metalation affords intermediate **IV** and following reductive elimination releases 3-arylcoumarin adduct. Although the exact role of TFAA is obscure, it is proved to be crucial for catalytic turnover.[15] It is anticipated that Ac_2O acetylates the Pd complex and regenerates $Pd(OAc)_2$ to render the C-H bond functionalization catalytic.



Scheme 2 A possible mechanism for direct arylation reactions

In summary, we have developed a versatile, regioselective and atom economical arylation of coumarins with simple unactivated arenes. This protocol provides an unprecedented approach to biologically interesting 3-arylcoumarins via palladium-catalyzed twofold C-H functionalization. It takes advantages of mild reaction conditions where the cross-coupling between two inert C-H bonds proceeds in absence of any acids. The presence of catalytic amounts of $Pd(OAc)_2$ in TFAA is adequate to afford desired arylated coumarins in good to high yields. The substrate scope is broad and further investigations to extend the substrate scope to heterocylces and more synthetic applications are under way.

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Notes and references

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